Amendments to the Specification

Additions are indicated by underlining (underlining).

Please replace the paragraph which spans page 14 (lines 27-31) through page 15 (lines 1-23) with the following amended paragraph:

Paired-related homeodomain proteins including SHOX preferentially bind to a palindromic sequence TAAT(N)$_n$ATTA [SEQ ID NO: 1], where to palindromic TAAT sequences are separated by two to four less significant nucleotides (N) (Wilson et al., 1993). This has also experimentally been demonstrated to hold true for SHOX (Rao et al, 2001). Interestingly, two of those palindromic sequences are present in the 5'flanking regulatory region of the BNP gene (accession number D.16641). The proximal one, TAATGAATTG [SEQ ID NO: 2], is 600 nucleotides upstream of the mRNA, further referred to as BNP-600, and the distal one, TAATGATAATTA [SEQ ID NO: 3], is -1220 nucleotides upstream, further referred to as BNP-1220. To demonstrate specific *in vitro* interaction of SHOX to these DNA sequences, we have performed electromobility shift assays (EMSA) with BNP-600 and BNP-1220 specific oligonucleotides. Electromobility shifts were observed at low protein concentration of 0.5 μM for both predicted binding sites, with a slightly higher affinity towards BNP-1220 as compared to BNP-600. Rise of the SHOX concentration to 0.5 and 3 μM led to the formation of homodimeric complexes. Again, a preference of the SHOX protein for BNP-1220 was observed which resulted in a dimeric complex at lower concentrations compared to BNP-600. In competition experiments no difference between the two sequences BNP-600 and BNP-1220 was detected; for both DNAs a minimum of 500-fold excess of cold oligonucleotide was necessary to completely inhibit the binding of SHOX. In supershift experiments a supershift of the signal was generated only in the presence of both SHOX and rabbit anti-human SHOX-3 antibody (AB) (Figures 2A and 3A). Furthermore, substitution of two nucleotides within the palindromic sequence almost completely abolished SHOX binding. Replacement of five nucleotides in the palindromic sequence led to an entire loss of SHOX binding, indicating the sequence specificity of this protein-DNA

interaction. These data strongly support the existence of (at least) two binding sites recognized by the SHOX protein in the regulatory region of BNP. BNP therefore is a direct target for the transcription factor SHOX.

Please replace the paragraph on page 19 (lines 2-10) with the following amended paragraph:

For quantitative real time (RT)-PCR analysis RNA extracted from cells was reverse transcribed as described before. The resulting first strand cDNA was used as template in PCR reactions. Primers for PCR were selected using the Primer3 software and checked for specificity by NCBI BLAST of the human genome. In addition to melting curve analysis the resulting PCR products were analyzed for specificity on agarose gels. The following primer pairs were used in PCR experiments: GAPDH: ACCACAGTCCATGCCATCAC [SEQ ID NO: 4], TCCACCACCCTGTTGCTGTA [SEQ ID NO: 5]; SHOX: ATGGAAGAGCTCACGGCTTTTGTATCC [SEQ ID NO: 6], GAAGAGTCGCTCGAGCTCGTTC [SEQ ID NO: 7]; BNP: TTCTTGCATCTGGCTTTCCT [SEQ ID NO: 8], ACCGTGGAAATTTTGTGCTC [SEQ ID NO: 9].

Please replace the paragraph which spans page 19 (lines 22-31) through page 20 (lines 1-11) with the following amended paragraph:

To create double stranded DNA for mobility shift assays two complementary oligonucleotides were annealed, generating 5' overhangs on each side to permit radiolabelling using the Taq polymerase. The following oligonucleotides were used in the shift experiments (only the forward strand of the probes are given, putative binding site in bold, mutagenized nucleotides underlined):

BNP-1220Wt:

TAATCACCAGGCCACCTGCTAATGATAATTAGATCATGGGTGGTCAGATG [SEQ ID

NO: 10]; BNP-1220a:

TAATCACCAGGCCACCTGC**TACTGATAACTA**GATCATGGGTGGTCAGATG [SEQ ID NO: 11]; BNP-1220b:

GGGTCACCAGGCCACCTGC**TGATGATAGTTA**GATCATGGGTGGTCAGATG [SEQ ID NO: 12]; BNP-1220c:

GGGTCACCAGGCCACCTGC**TCCCGATACCTA**GATCATGGGTGGTCAGATG [SEQ ID NO: 13]; BNP-600Wt:

TTCCTGGTCATACCCAGGCTTT**TAATGAATTG**CCACTGGGGAATCAGCAT [SEQ ID NO: 14]; BNP-600a:

GGG**TT**CCTGGTCATACCCAGGCTTTT**GATGAATGG**CCACTGGGGAATCAGCAT [SEQ ID NO: 15]; BNP-600b:

GGG**TT**CCTGGTCATACCCAGGCTTTT**GGGGAAGGG**CCACTGGGGAATCAGCAT [SEQ ID NO: 16].